

# Air Pollution and Progression of Atherosclerosis in Different Vessel Beds—Results from a Prospective Cohort Study in the Ruhr Area, Germany

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**OBJECTIVES:** Due to inconsistent epidemiological evidence on health effects of air pollution on progression of atherosclerosis, we investigated several air pollutants and their effects on progression of atherosclerosis, using carotid intima media thickness (cIMT), coronary calcification (CAC), and thoracic aortic calcification (TAC).

**METHODS:** We used baseline (2000–2003) and 5-y follow-up (2006–2008) data from the German Heinz Nixdorf Recall cohort study, including 4,814 middle-aged adults. Residence-based long-term air pollution exposure, including particulate matter (PM) with aerodynamic diameter  $\leq 2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ ), ( $\text{PM}_{10}$ ), and nitrogen dioxide ( $\text{NO}_2$ ) was assessed using chemistry transport and land use regression (LUR) models. cIMT was quantified as side-specific median IMT assessed from standardized ultrasound images. CAC and TAC were quantified by computed tomography using the Agatston score. Development (yes/no) and progression of atherosclerosis (change in cIMT and annual growth rate for CAC/TAC) were analyzed with logistic and linear regression models, adjusting for age, sex, lifestyle variables, socioeconomic status, and traffic noise.

**RESULTS:** While no clear associations were observed in the full study sample (mean age 59.1 ( $\pm 7.6$ ) y; 53% female), most air pollutants were marginally associated with progression of atherosclerosis in participants with no or low baseline atherosclerotic burden. Most consistently for CAC, e.g., a  $1.5 \mu\text{g}/\text{m}^3$  higher exposure to  $\text{PM}_{2.5}$  (LUR) yielded an estimated odds ratio of 1.19 [95% confidence interval (CI): 1.03, 1.39] for progression of CAC and an increased annual growth rate of 2% (95% CI: 1%, 4%).

**CONCLUSION:** Our study suggests that development and progression of subclinical atherosclerosis is associated with long-term air pollution in middle-aged participants with no or minor atherosclerotic burden at baseline, while overall no consistent associations are observed. <https://doi.org/10.1289/EHP7077>

## Background

Outdoor air pollution defines a global environmental risk factor for mortality (WHO Regional Office for Europe 2013; WHO 2009), and has been identified as leading contributor to the burden of disease worldwide (Gakidou et al. 2017). In particular, air pollution exposure contributes to the development of cardiovascular diseases (CVD) (Franklin et al. 2015; Rückerl et al. 2011). Although short-term exposure to particulate matter (PM) can trigger acute cardiovascular events, long-term exposure to PM was linked to the development of underlying chronic cardiovascular pathologies (Franklin et al. 2015), of which atherosclerosis is considered the major one (Künzli et al. 2011). Although experimental animal studies provide strong evidence for air pollution causing atherosclerosis through oxidative stress and systemic inflammation (Araujo et al. 2008; Soares et al. 2009; Sun et al. 2005), epidemiological evidence on air pollution effects on the

development and progression of atherosclerosis along the pathway to cardiovascular endpoints is less consistent (Adar et al. 2013; Gan et al. 2014; Hennig et al. 2019; Kaufman et al. 2016; Künzli et al. 2010; Wilker et al. 2013).

In epidemiological studies, the degree of atherosclerosis can be quantified by medical imaging [e.g., computed tomography (CT) or ultrasound] of the arteries, measuring coronary artery calcification (CAC), thoracic aortic calcification (TAC), and intima media thickness of the common carotid artery, which have all been identified as predictors of cardiovascular and cerebrovascular events (Defilippis et al. 2011; Den Ruijter et al. 2012; Erbel et al. 2010; Folsom et al. 2008; Geisel et al. 2017; Kälisch et al. 2017; Nair et al. 2012; Polak et al. 2011).

Due to ease of assessment, most epidemiological studies on air pollution and progression of atherosclerosis studied the change in cIMT (Adar et al. 2013; Gan et al. 2014; Kaufman et al. 2016; Künzli et al. 2010; Wilker et al. 2013). A meta-analysis, including three longitudinal studies, reported a positive association between particulate matter with an aerodynamic diameter less or equal than  $2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ ) and carotid intima media thickness (cIMT) (Provost et al. 2015), in line with a single longitudinal study reporting a positive association between black carbon and cIMT (Wilker et al. 2015). The most recent analyses conducted in the North American Multi-Ethnic Study of Atherosclerosis only found an association of ozone with cIMT (Wang et al. 2019), but not between  $\text{PM}_{2.5}$  or  $\text{NO}_2$  and cIMT progression (Kaufman et al. 2016). In contrast, the investigators observed positive association of  $\text{PM}_{2.5}$  and  $\text{NO}_2$  with CAC progression (Kaufman et al. 2016), but others did not (Dorans et al. 2016). TAC progression has been shown to be related to air pollution only in early stages of thoracic calcification, but not in more advanced stages of atherosclerosis (Hennig et al. 2019).

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Although all existing studies provide considerable sources of heterogeneity (outcome definitions, air pollutants and exposure modeling, study populations and statistical methods) that could explain inconsistent epidemiological findings, we aimed to comprehensively investigate effects of air pollution on the development and progression of atherosclerosis. To that end, we investigated progression of atherosclerosis in three different vessel beds (coronary circulation, thoracic aorta, and carotid arteries) applying different imaging methods (CT and ultrasound) in participants from the Heinz Nixdorf Recall (HNR) cohort study. To investigate possible reasons for heterogeneity between studies due to selection of study populations, and motivated by our prior findings of stronger associations at lower baseline levels of atherosclerosis, we investigated subgroup effects based on atherosclerosis burden at baseline (t0) and explored individual susceptibility factors. Furthermore, we made use of two complementary air pollution exposure models, yielding *a*) point-specific estimates [land use regression (LUR) modeling], which capture small-scale differences in air pollution exposure specifically related to traffic, and *b*) urban background exposure [chemistry transport modeling (CTM)], which captures changes over time. Finally, we took ambient noise exposure into account, a potential confounder within the air pollution and cardiovascular framework (Münzel et al. 2018).

## Methods

### Study Design

The HNR (Risk Factors, Evaluation of Coronary Calcification, and Lifestyle) study is a population-based prospective cohort study, including 4,814 randomly selected participants of 45 to 75 years of age at baseline (t0: 2000–2003) from three large adjacent cities (Mülheim, Essen, and Bochum) in the metropolitan Ruhr area of Germany [recruitment efficacy proportion: 55.8%; (Stang et al. 2005)]. The study design has been described in detail elsewhere (Schmermund et al. 2002). The study was approved by the institutional ethics committees of the University of Duisburg-Essen and the University Hospital of Essen and adhered to strict internal and external quality assurance protocols. The follow-up examination (t1: 2006–2008) had a response of 86.4% ( $n = 4,157$ ). Assessment for both examinations included a self-administered questionnaire, face-to-face interviews for personal risk factor assessment and clinical examinations, and comprehensive laboratory tests according to standard protocols. All participants gave informed consent.

### Exposure Assessment

Long-term exposure to residential ambient air pollution was assessed using concentrations of particulate matter (PM) with an aerodynamic diameter  $\leq 2.5 \mu\text{m}$  [ $\text{PM}_{2.5}$  ( $\mu\text{g}/\text{m}^3$ )], and  $\leq 10 \mu\text{m}$  [ $\text{PM}_{10}$  ( $\mu\text{g}/\text{m}^3$ )], the number of accumulation mode particles  $\text{PN}_{\text{acc}}$  (#/mL),  $\text{PM}_{2.5 \text{ abs}}$  absorbance [ $\text{PM}_{2.5 \text{ abs}}$  ( $\mu\text{g}/\text{m}^3$ )], and nitrogen dioxide [ $\text{NO}_2$  ( $\mu\text{g}/\text{m}^3$ )]. To reflect long-term urban background exposure differences within our study area, we estimated mean long-term air pollution concentrations for  $\text{PM}_{2.5}$ ,  $\text{PM}_{10}$ ,  $\text{PN}_{\text{acc}}$ , and  $\text{NO}_2$  in a spatial grid of  $1 \times 1 \text{ km}^2$  assigned to participant's addresses (Nonnemacher et al. 2014), using the European Air pollution Dispersion chemistry transport model (EURAD-CTM, short: CTM). The EURAD-CTM uses input data from official emission inventories (i.e., traffic, industry, agriculture, energy production, etc.) (European Environment Agency 2011) data on meteorology and regional topography, in combination with modeling the dispersion, chemical reactivity, and mass transport between horizontal strata and deposition to calculate daily exposure concentrations in a  $1 \times 1 \text{ km}^2$  grid (Memmesheimer et al. 2004). The EURAD-CTM includes data assimilation on an hourly basis for routinely measured

air pollutants ( $\text{PM}_{10}$ ,  $\text{NO}_2$ ), using routine monitoring data in North Rhine-Westphalia (NRW) provided by the local environmental agency (State Agency for Nature, Environment, and Consumer Protection, LANUV-NRW). For this study, daily concentrations were assessed during the examination years (2000–2003 and 2006–2008), which were assigned to participants' baseline and follow-up addresses using a geographic information system. Because model data from 2004 to 2005 were not available, long-term exposure was calculated as the mean of all daily values over both examination periods (2000–2003 and 2006–2008).

In addition, annual exposure to  $\text{PM}_{2.5}$ ,  $\text{PM}_{10}$ ,  $\text{PM}_{2.5 \text{ abs}}$ , and  $\text{NO}_2$  at point of participants' residences was estimated using land use regression (LUR) models that were locally developed as part of the European Study of Cohorts on Air Pollution Effects using a standardized protocol (Beelen et al. 2013; Eeftens et al. 2012). Each LUR model was locally cross-validated with the leave-one-out-cross-validation (LOOCV). Resulting explained variances (adjusted  $R^2$ ) (and LOOCV- $R^2$ ) within the Ruhr Area were 85% (79%) for predicting  $\text{PM}_{2.5}$ , 66% (59%) for predicting  $\text{PM}_{10}$ , 97% (95%) for predicting  $\text{PM}_{2.5 \text{ abs}}$ , and 88% (82%) for predicting  $\text{NO}_2$  (Beelen et al. 2013; Eeftens et al. 2012). The overall agreement between long-term urban background concentrations (estimated with the EURAD-CTM) and point-specific concentrations (estimated with the ESCAPE LUR) was moderate to low (Spearman correlations  $< 0.45$ ), reflecting different aspects of the air pollution exposure conditions within a densely populated and industrialized urban area (de Hoogh et al. 2014; Hennig et al. 2016).

### Assessment of the Outcomes

cIMT was assessed by B-mode ultrasound (Vivid FiVe, GE Ultrasound Europe), using a linear array 10-MHz scan head, at the left and right common carotid artery (Bauer et al. 2009). The semiautomatic computer-based software Artery Measurement (AMS) II (version 1.151; Chalmers University of Technology) (Wendelhag et al. 1997) was used to determine median cIMT per ultrasound image (exported offline as bitmap file) at the far wall within the first 10 mm proximal to the bulb. To reduce measurement error, images were grouped into work packages of approximately 200 images, including 10 repeated images each, to monitor intrareader variability. If mean intrareader variability was  $> 0.03 \text{ mm}$ , the respective reader was trained again and the corresponding work package had to be remeasured to achieve high quality measurement data. Offline measurements were performed by six certified readers according to a standardized operation procedure.

Mean side-specific cIMT value (millimeters) for baseline and 5-y follow-up was calculated based on the median values of all available images for each examination. Progression (yes/no) was operationalized as  $\text{cIMT}_{t1} - \text{cIMT}_{t0} > 0$ , and the extent of progression was assessed as annual  $\mu\text{m}$ -change in cIMT:  $\Delta\text{cIMT} = (\text{cIMT}_{t1} - \text{cIMT}_{t0}) / \text{follow-up time}$  for the left and right body side. An early stage (no/minor) vs. a more advanced stage of atherosclerotic burden at baseline was defined by dichotomizing at a cut point of  $0.7 \text{ mm}$  ( $\leq 0.7$  vs.  $> 0.7 \text{ mm}$ ), which was identified as the upper value of a normal cIMT range for middle-aged adults (O'Leary et al. 1999).

Participants underwent cardiac CT as part of the primary study aim of the HNR Study. CAC and TAC were derived from non-contrast-enhanced electron-beam CT scans, using a C-100 (t0) and C-150 (t1) scanner (GE, Imatron), following a standardized methodology for acquisition and interpretation of the scans, which has been reported previously (Erbel et al. 2010; Schmermund et al. 2002). The CTs were operated in the single-slice (3 mm) mode with an image acquisition time of 100 ms. The Agatston algorithm was used for quantification of calcification, identifying a calcified lesion as at least 4 contiguous pixels

with a CT density  $\geq 130$  Hounsfield (Agatston et al. 1990). Analyses were performed using a Virtuoso workstation (Siemens Medical Solutions). The total CAC score was calculated, comprising all calcified lesions in the coronary system. A reassessment of CAC scoring was implemented as quality control when extreme progression or regression was observed (Lehmann et al. 2018). The total TAC score was calculated, comprising all calcified lesions, including segments of the ascending and descending portion of the thoracic aorta that were visible in the CT scan (Kälsch et al. 2013b). Progression (yes/no) of CAC and TAC was operationalized as  $CAC_{t1} - CAC_{t0} > 0$  and  $TAC_{t1} - TAC_{t0} > 0$ , respectively. Due to its exponential nature, extent of progression was assessed as the annual growth rate in Agatston score:  $(\log(CAC_{t1} + 1) - \log(CAC_{t0} + 1))/\text{years of follow-up}$  (Lehmann et al. 2018) and  $(\log(TAC_{t1} + 1) - \log(TAC_{t0} + 1))/\text{years of follow-up}$  respectively (Kälsch et al. 2017). A beta-coefficient of 0.01 in the linear regression model can be interpreted as an exposure-related 1% increase in annual growth rate. An early stage (no/minor) vs. a more advanced stage of atherosclerotic burden at baseline was defined by dichotomizing at cut point 10 (no/minor calcification 0–9 Agatston score units vs. more extensive calcification  $\geq 10$  Agatston score units).

### Definition of Covariates

Long-term road traffic noise was modeled for the year 2006 according to the European Union Directive 2002/49/EC (EU 2008) and the validated national calculation method VBUS/RLS-90 (28) for the year 2006 (supplied from the city administrations), considering small-scale topography of the area, dimensions of buildings, noise barriers, first order reflections, street axis, measured or estimated vehicle-type specific traffic density for all roads, speed limit, and type of street surface. Average traffic noise values [A-weighted dB(A)] day–evening–night (24 h) noise (Lden) at the participant's residence was estimated at a height of  $4 \pm 0.2$  m selecting the highest estimated noise level within a buffer of 10 m from the residence.

Individual socioeconomic status (SES) was defined as years of education in four categories ( $\leq 10$ , 11–13, 14–17,  $\geq 18$  y) according to the International Standard Classification of Education (UNESCO 1997). Neighborhood SES (nSES) was assessed by unemployment rate (%) for each administrative neighborhood (median size: 11,263 inhabitants) obtained from local census authorities for t0 (2000–2003) (Dragano et al. 2009). Smoking status was defined as current, ex- ( $> 1$  y since quitting), and never-smoker. Lifetime cumulative smoking was assessed in pack-years at baseline. Exposure to environmental tobacco smoke (ETS) referred to ETS at home, at work, or in other places. Physical activity (yes/no) was assessed as regular sporting activities at least once a week for a minimum of 30 min. Alcohol consumption was operationalized as drinks per week. Anthropometric measurements (height, weight) were conducted according to standardized protocols to calculate the body mass index [BMI ( $\text{kg}/\text{m}^2$ )]. Diabetes mellitus (DM) was defined as prior physician diagnosis of diabetes or taking an anti-diabetic drug or having a blood glucose  $\geq 200$  mg/dL or having a fasting blood glucose  $\geq 126$  mg/dL. High-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, and high sensitivity C-reactive protein (hs-CRP) (all mg/dL) were measured with standard methods at the central laboratory of the University Hospital of Essen. In the analysis, we used quotient of LDL-C and HDL-C (LDL-C/HDL-C). Confirmed medication taken in the previous 7 d was assigned using the WHO Anatomical Therapeutic Chemical classification system (ATC) (WHO 2013). Blood pressure was calculated as the mean of the second and third of three measurements, using an oscillometric method according to a standard protocol. Hypertension was defined as systolic or diastolic

blood pressure of 140 mmHg or greater or 90 mmHg or greater, respectively, or use of antihypertensive medication. Incident coronary heart disease (CHD) was based on self-reported incident coronary events that met predefined study criteria (Schmermund et al. 2002) and which were adjudicated with medical records by a study end point committee (Erbel et al. 2010). Updated information on all baseline characteristics were obtained at the first follow-up examination, with the exception of neighborhood unemployment rate, education, and cumulative smoking exposure, which were only obtained at baseline. Traffic was assessed as distance (in meters) to high-traffic roads [i.e., roads with a traffic count of  $> 26,000$  vehicles/day (upper quintile of traffic density)], using official digitized maps with a precision of at least 0.5 m and the median strip between the oncoming traffic lanes as reference.

### Analytic Strategies

The statistical analysis was conducted in the study sample with participants of the baseline and first follow-up examination, free of CHD at baseline ( $n = 3,907$ ), available exposure data for the complete follow-up ( $n = 3,753$ ), nonmissing data on progression of atherosclerosis for at least one marker ( $n = 3,625$ ) and nonmissing covariate data ( $n = 3,480$ ) (Figure S1). Due to different sample sizes for atherosclerosis markers, the main analysis was conducted in marker-specific subsamples. For the analysis of cIMT, 2,116 participants had nonmissing information on left cIMT, 2,197 had nonmissing data on right cIMT, 3,220 had nonmissing data on CAC, and 3,126 had nonmissing data on TAC.

We a) used logistic regression models to estimate odds ratios [OR; and 95% confidence intervals (CI)] for progression (yes/no) per interquartile range (IQR) increase in air pollutant concentration; and b) estimated the effect of an IQR increase in concentrations of air pollution on annual change of atherosclerosis (wall thickening and growth rate of calcification), using linear regression models. All models were estimated for each marker separately in the total study population and in subgroups of participants with no/minor vs. advanced atherosclerotic burden at baseline. Subgroup effects were estimated by adding the subgroup indicator and an interaction term between the continuous exposure and the subgroup indicator. c) We estimated the 5-y risk of incident calcification in the coronaries and the thoracic aorta with logistic regression.

Confounder adjustment was based on a hypothesized directed acyclic graph (DAG; Figure S2), a qualitative method emphasized by Greenland et al. (1999), complemented with a quantitative evaluation of suggested minimal sufficient adjustment sets and covariate extensions (Figures S3 and S4). Our main model included age, sex, BMI, smoking status and quantity, environmental tobacco smoke (ETS), LDL-C/HDL-C, physical activity, education, traffic noise, and for dichotomous outcomes additionally years of follow-up. Moreover, we investigated extended models including nSES and city.

In a separate step, we added potentially mediating covariates along the hypothesized pathway linking air pollution to atherosclerosis as covariates to the analysis. These covariates included baseline atherosclerosis, incident intake of statins during follow-up, hs-CRP, blood pressure, prevalent and incident hypertension, and prevalent and incident DM.

We also investigated effect modification by categorized personal risk factors, including sex (male vs. female), age ( $\leq 65$  y old vs.  $> 65$  y old), BMI ( $\leq 30$  vs.  $> 30$ ), DM (yes vs. no), incident statin intake (yes vs. no), low education ( $\leq 10$  y vs.  $> 10$  y), smoking (current vs. ex- and never-smoker), and high cardiovascular risk defined using Framingham risk score. Effect modification was investigated using interaction terms between categorical characteristics as described above and the respective continuous

exposure in the main model. Effect estimates were evaluated visually based on 95% CIs.

Sensitivity analyses included a more conservative cut point to identify progression (yes/no) in subclinical markers, namely 10% and 20% instead of 0. We conducted Poisson regression as an alternative approach to logistic regression to prevent overestimation of the relative risk (RR) in the highly frequent outcome. Moreover, we investigated an alternative metric of CAC progression, namely faster progression compared with internal expected reference values, defined by the percentile of CAC at baseline [ $CAC_{\text{expected}_t1} - CAC_{\text{observed}_t1} < 0$  (Lehmann et al. 2018)], which was based on the hypothesis that the individual's CAC progresses exponentially with time, similar to CAC percentiles with age. We also investigated mean cIMT progression considering the mean of both (left and/or right) side.

In addition, we investigated whether a different time window of exposure (namely, baseline exposure (2001–2003), as well as mean exposure between 2006 and 2008, estimated by the EURAD-CTM), affected our main results. We also estimated exposure effect estimates for subgroups less likely affected by exposure misclassification due to mobility using employment status (nonemployees or part-time employees working  $\leq 15$  h/wk vs. full-time employees), and due to change of residence prior to baseline (nonmovers vs. movers).

## Results

Out of 3,480 participants free of CAD at baseline with two valid measurements (one at baseline and one at follow-up examination) for at least one marker of subclinical atherosclerosis, complete exposure information and nonmissing covariate data, marker-specific subsamples were quite homogeneous with regard to personal characteristics (BMI, smoking status, education, or physical inactivity) (Table 1), including roughly 53% women and a mean age  $\sim 59.0$  [standard deviation (SD) 7.6] years of age at baseline.

Air pollutant concentrations at baseline were below current European air quality limit values, but clearly higher than World Health Organization recommendations (Table 2). Correlations between air pollutants were mostly moderate to high (Table 2). LUR modeling estimated higher long-term particle concentrations, but lower  $\text{NO}_2$  concentrations than CTM (Figure S5). Mean air pollutant concentrations estimated by CTM decreased for all pollutants (Figure S6) during the follow-up period with overall high correlations between examination periods ( $>0.87$ ) (Table S1).

Mean baseline cIMT (left) was 710.9 (172.1)  $\mu\text{m}$  with a calculated annual change of 21.1 (31.9)  $\mu\text{m}$ , resulting in 78% participants with positive progression after 5 y (Table 1, Figure S7). Mean baseline cIMT (right) was 693.3 (168.9)  $\mu\text{m}$  with a calculated annual change of 21.5 (29.8)  $\mu\text{m}$ , resulting in 81% participants with progression after 5 y. Median baseline CAC was 7.2 (IQR 0.0–88.2) Agatston Score units with an observed annual growth rate of 0.106 (SD 0.225) and 60% progression after 5 years of follow-up. Incident CAC was observed in 25.7% participants with no CAC add baseline ( $n = 1,154$ ). Median baseline TAC was 16.0 (IQR 0.0–108.3) Agatston Score units with an observed annual growth rate of 0.091 (SD 0.470) and 53% progression after 5 years of follow-up. Incident TAC was observed in 42.2% participants with no TAC add baseline ( $n = 1,161$ ). In all four markers, overall progression was more pronounced in participants with no or minor atherosclerotic burden (Figure S8).

### Air Pollution and Progression of Atherosclerosis

In the full sample analysis, we observed no clear pattern of an association between any of the air pollutants and progression or

degree of progression of atherosclerosis. Although most effect estimates for the crude and main (noise-adjusted) were positive, CI were wide and included the null effect (Figure 1, with complementing numbers in Table S2). Additional covariate adjustment (residence and nSES) as covariates did not substantially change effect estimates (Figures S3 and S4), nor did including potential mediating factors (Figures S9 and S10).

Baseline level of subclinical atherosclerosis had an impact on the association of air pollutants with progression of atherosclerosis (Figure 1 with complementing numbers in Tables S3). Most consistently,  $\text{PM}_{10}$ ,  $\text{PM}_{2.5}$ ,  $\text{PN}_{\text{acc}}$ , and  $\text{NO}_2$  modeled by CTM were related to progression of left cIMT, CAC, and TAC in participants with no or minor burden of atherosclerosis at baseline (e.g., an estimated OR of 1.12 [0.96, 1.31] for progression of CAC per 3.8  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$ ).  $\text{PM}_{10}$  and  $\text{PM}_{2.5}$  modeled by LUR were associated with left cIMT and CAC [e.g., a 1.5  $\mu\text{g}/\text{m}^3$  higher exposure to  $\text{PM}_{2.5}$  (LUR) yielded an estimated OR of 1.19 (95% CI: 1.03, 1.39) for progression of CAC and an increased annual growth rate of 2% (95% CI: 1%, 4%)]. On the other hand, effect estimates for participants with more advanced atherosclerotic burden yielded inverse or null findings, most notably for TAC. For right cIMT, we observed no consistent associations across pollutants and outcome definition with regard to atherosclerotic burden at baseline. Supporting findings in participants with no or minor atherosclerotic burden, long-term air pollution exposure was consistently related to incident CAC, whereas CI for incident TAC were elevated but most often included the null (Table 3).

We did not observe clear and consistent effect modification by personal characteristics (Figure S11). In general, we found a pattern of stronger associations in participants who had diabetes, participants who were obese, and less-educated participants, whereas the analysis of cIMT suggests possible inverse associations in participants with a high baseline Framingham Risk Score and participants with incident statin intake during the follow-up period.

### Sensitivity Analyses

Results of evaluating progression with a more conservative cut point of 10% change (and 20%) did not differ notably from the main results (Table S4). The alternative approach of applying a Poisson regression to estimate RR instead of OR, as expected, yielded smaller point estimates yet did not change our main conclusions (Table S4). Investigating progression of mean of left and/or right cIMT as expected yielded less consistent findings, and evaluating whether CAC progressed faster than following the expected percentile did not change the observed main findings (Table S5).

Inspecting different time windows of air pollutant exposures separately did not differ from the main approach of combining exposure time windows to one long-term exposure measure (Table S6). Exploring exposure misclassification based on variables of personal mobility and relocation prior to baseline showed that estimated effects were quite stable in the group of nonemployees and nonmovers (Figure S13).

## Discussion

In this study of middle-aged adults in Germany, our analysis shows no consistent associations of long-term exposure to ambient particulate and gaseous air pollutants with the development and progression of atherosclerosis in different vessels beds in the full sample over a follow-up time of roughly 5 y. However, in those participants with no or only minor atherosclerotic burden at baseline, we observed associations of long-term exposure to

**Table 1.** Summary statistics for outcome-specific subpopulations within the Heinz-Nixdorf Recall Study sample at baseline unless otherwise indicated. Continuous variables with a symmetric distribution are displayed using mean  $\pm$  standard deviation (SD), continuous variables with a skewed distribution are displayed using median (Q1, Q3), and categorical variables are displayed by absolute and relative frequencies [*n* (%)].

Variable	Value	cIMT (left) <i>n</i> = 2,116	cIMT (right) <i>n</i> = 2,197	CAC <i>n</i> = 3,220	TAC <i>n</i> = 3,126
cIMT, t0 ( $\mu$ m)	—	710.9 $\pm$ 172.1	693.3 $\pm$ 168.9	—	—
cIMT, t1 ( $\mu$ m)	—	817.2 $\pm$ 185.4	801.9 $\pm$ 161.1	—	—
Change in cIMT ( $\mu$ m)	—	21.1 $\pm$ 31.9	21.5 $\pm$ 29.8	—	—
cIMT progression	No	465 (22.0%)	426 (19.4%)	—	—
	Yes	1,651 (78.0%)	1,771 (80.6%)	—	—
Calcification, t0 (Agatston score)	—	—	—	7.2 (0.0, 88.2)	16.0 (0.0, 108.3)
Calcification, t1 (Agatston score)	—	—	—	26.8 (0.0, 193.9)	29.5 (0.0, 307.1)
Change in calcification (growth rate)	—	—	—	0.106 $\pm$ 0.225	0.091 $\pm$ 0.470
Calcification progression	No	—	—	1,291 (40.1%)	1,466 (46.9%)
	Yes	—	—	1,929 (59.9%)	1,660 (53.1%)
Incident calcification <sup>a</sup>	No	—	—	857 (26.6%)	671 (21.5%)
	Yes	—	—	297 (9.2%)	490 (15.7%)
Age (y)	—	58.9 $\pm$ 7.5	58.9 $\pm$ 7.6	59.0 $\pm$ 7.6	59.1 $\pm$ 7.6
Sex	Female	1,109 (52.4%)	1,156 (52.6%)	1,726 (53.6%)	1,663 (53.2%)
	Male	1,007 (47.6%)	1,041 (47.4%)	1,494 (46.8%)	1,463 (46.8%)
Education	$\leq$ 10 y	204 (9.6%)	208 (9.5%)	318 (9.9%)	310 (9.9%)
	$\geq$ 18 y	256 (12.1%)	266 (12.1%)	363 (11.3%)	349 (11.2%)
	11–13 y	1,169 (55.2%)	1,215 (55.3%)	1,821 (56.6%)	1,767 (56.5%)
	14–17 y	487 (23.0%)	508 (23.1%)	718 (22.3%)	700 (22.4%)
Unemployed rate (2001) (%)	—	12.5 $\pm$ 3.4	12.4 $\pm$ 3.4	12.4 $\pm$ 3.4	12.4 $\pm$ 3.4
Smoking status	Current smoker	481 (22.7%)	500 (22.8%)	729 (22.6%)	698 (22.3%)
	Ex-smoker	688 (32.5%)	717 (32.6%)	1,036 (32.2%)	1,026 (32.8%)
	Never smoker	947 (44.8%)	980 (44.6%)	1,455 (45.2%)	1,402 (44.8%)
Cumulative smoking (pack-years)	—	2.4 (0.0, 21.0)	2.7 (0.0, 21.8)	2.2 (0.0, 22.0)	2.4 (0.0, 22.0)
ETS (any exposure)	No	1,389 (65.6%)	1,437 (65.4%)	2,084 (64.7%)	2,039 (65.2%)
	Yes	727 (34.4%)	760 (34.6%)	1,136 (35.3%)	1,087 (34.8%)
Physical inactivity	No	1,196 (56.5%)	1,241 (56.5%)	1,809 (56.2%)	1,756 (56.2%)
	Yes	920 (43.5%)	956 (43.5%)	1,411 (43.8%)	1,370 (43.8%)
BMI (kg/m <sup>2</sup> )	—	27.4 $\pm$ 4.4	27.4 $\pm$ 4.4	27.4 $\pm$ 4.4	27.6 $\pm$ 4.3
LDL-C (mg/dL)	—	146.5 $\pm$ 36.5	146.7 $\pm$ 35.8	146.2 $\pm$ 35.6	146.4 $\pm$ 35.7
HDL-C (mg/dL)	—	59.7 $\pm$ 17.4	59.5 $\pm$ 17.4	59.3 $\pm$ 17.1	59.3 $\pm$ 17.3
Statin medication <sup>a</sup>	No	1,902 (89.9%)	1,983 (90.3%)	2,805 (87.1%)	2,719 (87.0%)
	Yes	160 (7.6%)	152 (6.9%)	216 (6.7%)	215 (6.9%)
Incident statin use <sup>a</sup>	No	1,846 (87.2%)	1,896 (86.3%)	2,723 (84.6%)	2,603 (83.3%)
	Yes	216 (10.2%)	239 (10.9%)	298 (9.3%)	331 (10.6%)
Hs-CRP (mg/dL) <sup>a</sup>	—	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)
Framingham Risk <sup>a</sup>	High	237 (11.2%)	244 (11.1%)	399 (12.4%)	398 (12.7%)
	Low	1,197 (56.6%)	1,229 (55.9%)	1,802 (56.0%)	1,715 (54.9%)
	Mediate	680 (32.1%)	723 (32.9%)	1,019 (31.6%)	1,012 (32.4%)
Hypertension <sup>a</sup>	No	1,034 (48.9%)	1,079 (49.1%)	1,515 (47.0%)	1,464 (46.8%)
	Yes	1,080 (51.0%)	1,117 (50.8%)	1,705 (53.0%)	1,661 (53.1%)
Incident hypertension <sup>a</sup>	No	688 (32.5%)	699 (31.8%)	988 (30.7%)	951 (30.4%)
	Yes	345 (16.3%)	380 (17.3%)	526 (16.3%)	512 (16.4%)
Diabetes	No	1,895 (89.6%)	1,954 (88.9%)	2,853 (88.6%)	2,764 (88.4%)
	Yes	221 (10.4%)	243 (11.1%)	367 (11.4%)	362 (11.6%)
Incident type 2 diabetes <sup>a</sup>	No	1,740 (82.2%)	1,798 (81.8%)	2,617 (81.3%)	2,529 (80.9%)
	Yes	155 (7.3%)	156 (7.1%)	236 (7.3%)	235 (7.5%)
Developed coronary heart disease	No	2,056 (97.2%)	2,126 (96.8%)	3,205 (99.5%)	3,051 (97.6%)
	Yes	60 (2.8%)	71 (3.2%)	15 (0.5%)	75 (2.4%)
Lden [dB(A)]	—	53.9 $\pm$ 9.4	53.8 $\pm$ 9.4	53.9 $\pm$ 9.3	53.9 $\pm$ 9.3
Distance to highly trafficked road (m)	—	1,018.0 $\pm$ 808.7	1,033.2 $\pm$ 817.2	1,023.7 $\pm$ 811.3	1,025.5 $\pm$ 818.4

<sup>a</sup>Including additional missing values. For subpopulation of cIMT (left): Statin medication (*n* = 54), Incident statin use (*n* = 54), Hs-CRP [mg/dL] (*n* = 5), Framingham Risk (*n* = 2), Hypertension (*n* = 2), Incident hypertension (*n* = 1,083), Incident type 2 diabetes (*n* = 221). For subpopulation of cIMT (right): Statin medication (*n* = 62), Incident statin use (*n* = 62), Hs-CRP (mg/dL) (*n* = 6), Framingham Risk (*n* = 1), Hypertension (*n* = 1), Incident hypertension (*n* = 1,118), Incident type 2 diabetes (*n* = 243). For subpopulation of CAC: Statin medication (*n* = 199), Incident statin use (*n* = 199), Hs-CRP (mg/dL) (*n* = 8), Incident hypertension (*n* = 1,706), Incident type 2 diabetes (*n* = 367), Incident calcification (*n* = 2,066). For subpopulation of TAC: Statin medication (*n* = 192), Incident statin use (*n* = 192), Hs-CRP (mg/dL) (*n* = 8), Framingham Risk (*n* = 1), Hypertension (*n* = 1), Incident hypertension (*n* = 1,663), Incident type 2 diabetes (*n* = 362), Incident calcification (*n* = 1,965). —, no data.

particulate air pollution with progression of atherosclerosis, whereas estimated effects in the group with more advanced atherosclerotic burden at baseline were null or inverse.

Long-term air pollution has been shown to be associated with cerebrovascular and cardiovascular events in multiple studies (U.S. EPA 2019; WHO 2013), including prior analyses of the HNR Study (Hoffmann et al. 2015). Therefore, our findings are important regarding the underlying hypothesis that ambient air pollution may lead to atherosclerosis on the pathway to CVD, possibly explaining the higher incidence and prevalence of cardiovascular and cerebrovascular disease observed in people with

higher air pollution exposure. Our findings of associations limited to earlier stages of atherosclerosis point to a higher susceptibility to air pollution in the development of atherosclerosis, which has also been observed in our prior analysis of environmental tobacco smoke and CAC (Peinemann et al. 2011). In contrast, our findings did not support a susceptibility to air pollution exposure in people with a higher cardiac risk profile based on personal characteristics or with an advanced burden of atherosclerosis. These findings are in line with investigations based on the Framingham Heart Study, which also found null or inverse estimates in analyses of participants with apparent calcifications at baseline

**Table 2.** Summary statistics [mean  $\pm$  standard deviation (SD)] of air pollutant concentrations (CTM during enrollment periods 2001–2003 and 2006–2008 and LUR) and pairwise Spearman correlation coefficients, estimated in 3,480 participants of the Heinz Nixdorf Recall Study population.

Exposure	Mean $\pm$ SD	IQR	PM <sub>10</sub> (LUR)	PM <sub>2.5</sub> (CTM)	PM <sub>2.5</sub> (LUR)	PN <sub>acc</sub> (CTM)	PM <sub>2.5abs</sub> (LUR)	NO <sub>2</sub> (CTM)	NO <sub>2</sub> (LUR)
PM <sub>10</sub> (CTM) ( $\mu\text{g}/\text{m}^3$ )	20.3 $\pm$ 2.6	3.8	0.33	0.86	0.56	0.79	0.35	0.62	0.5
PM <sub>10</sub> (LUR) ( $\mu\text{g}/\text{m}^3$ )	27.8 $\pm$ 1.9	2.1		0.18	0.89	0.46	0.9	0.34	0.55
PM <sub>2.5</sub> (CTM) ( $\mu\text{g}/\text{m}^3$ )	16.7 $\pm$ 1.3	2.0			0.38	0.72	0.14	0.69	0.4
PM <sub>2.5</sub> (LUR) ( $\mu\text{g}/\text{m}^3$ )	18.4 $\pm$ 1.1	1.5				0.73	0.89	0.46	0.66
PN <sub>acc</sub> (CTM) (#/mL)	3,408.4 $\pm$ 387.6	527.5					0.55	0.74	0.56
PM <sub>2.5abs</sub> (LUR) (0.0001/m)	1.6 $\pm$ 0.4	0.4						0.34	0.63
NO <sub>2</sub> (CTM) ( $\mu\text{g}/\text{m}^3$ )	39.5 $\pm$ 4.0	5.4							0.41
NO <sub>2</sub> (LUR) ( $\mu\text{g}/\text{m}^3$ )	30.2 $\pm$ 4.9	6.2							

Note: CTM, chemistry transport modeling; IQR, interquartile range; LUR, land use regression.

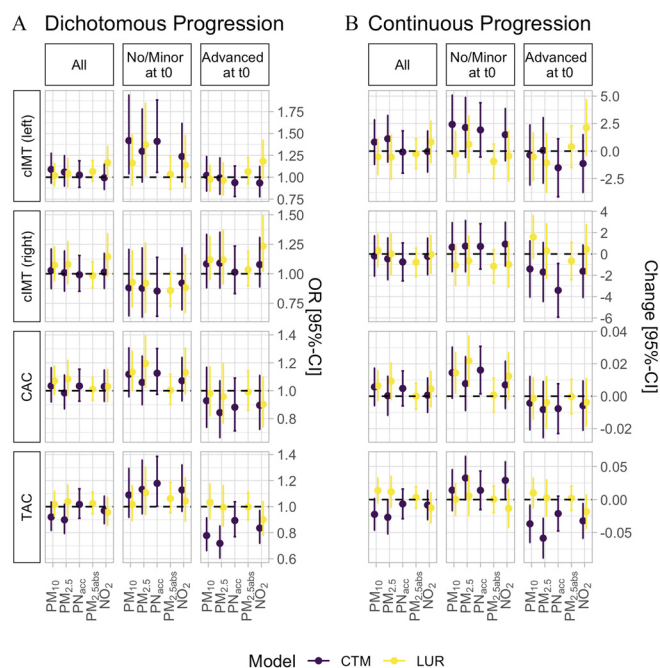
(Dorans et al. 2016, 2017). One explanation for inverse associations in participants with advanced atherosclerosis at baseline could be the dominating effect of cardioprotective therapy, which is more common in participants with advanced atherosclerosis.

However, not all vessel beds and their markers of subclinical atherosclerosis were equally susceptible to the effects of long-term exposure to air pollution. We observed the most consistent associations for progression of CAC (dichotomous progression, annual growth rate, and incidence) and for the left cIMT. Although side-specific differences in cIMT have been mentioned in literature before (Foerch et al. 2003; Luo et al. 2011), we

cannot explain the observed differences between left and right cIMT with regard to air pollution exposure, but we speculate that there could be different turbulence patterns leading to a higher susceptibility of the left common carotid vessel wall. Overall, results for cIMT vary greatly across studies (Perez et al. 2015). Only a few studies have investigated the association of air exposure with progression of cIMT, and these studies find striking differences in annual progression—from a mean of 1–5  $\mu\text{m}/\text{y}$  in a selected group of participants in atherosclerosis prevention trials (Künzli et al. 2010), 10–13  $\mu\text{m}/\text{y}$  in the MESA cohort (Wang et al. 2019), and 22  $\mu\text{m}/\text{y}$  in general population of the HNR Study reported here. In addition to biological characteristics and medical interventions, assessment methods regarding location, technique, and inclusion of plaque, as well as different consideration of body side (using mean of left and right cIMT or only right cIMT), contribute to these differences and possibly mask associations with air pollution.

Fewer but also inconsistent results can be found for investigations of long-term air pollution exposure and development and progression of CAC or aortic calcification. Kaufman et al. (2016) and Wang et al. (2019) both observed associations of PM<sub>2.5</sub> and NO<sub>2</sub> with CAC progression. Wang et al. (2019) found similar results for long-term exposure to high levels of ozone. Two analyses of the Framingham Heart Study investigating progression of coronary and aortic calcification do not find any association with roadway proximity or PM<sub>2.5</sub> (Dorans et al. 2016, 2017), whereas we had already observed associations restricted to participants with no or only minor manifestation of TAC at baseline in our prior study (Hennig et al. 2019).

Despite the fundamental differences in the applied exposure models, we observed generally similar patterns of associations with subclinical atherosclerosis for both models, strengthening the fact that our findings are not dependent on a specific air



**Figure 1.** Main effect estimates for the associations between different air pollutants and progression of atherosclerosis in subpopulations of the Heinz Nixdorf Recall Study based on the marker of atherosclerosis, investigating all participants (cIMT (left) = 2,116, cIMT (right) = 2,197, CAC = 3,220, TAC = 3,126), participants with no/minor atherosclerotic burden at baseline (t0) (cIMT (left) = 1,054, cIMT (right) = 1,017, CAC = 1,527, TAC = 1,761), and participants with advanced atherosclerotic burden at t0 (cIMT (left) = 1,203, cIMT (right) = 1,317, CAC = 1,693, TAC = 1,469). Main model is adjusted for age, sex, BMI, smoking status and quantity, ETS, LDL-C/HDL-C, physical activity, education, traffic noise and for dichotomous outcomes additionally years of follow-up. (A) This panel displays OR (95% CI) for any progression in atherosclerosis based on an IQR in exposure. (B) This panel displays change in thickness ( $\mu\text{m}$ ) for cIMT and change in growth rate for CAC and TAC (complementing numbers are in Tables S2 and S3). Note: BMI, body mass index; CAC, coronary artery calcification; CI, confidence interval; cIMT, carotid intima media thickness; ETS, environmental tobacco smoke; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; TAC, thoracic aortic calcification.

**Table 3.** Estimated odds ratio (95% CI) for incident CAC and TAC displayed per interquartile ranges of exposure based on participants of the Heinz-Nixdorf Recall Study sample ( $n = 1,154$  for CAC,  $n = 1,161$  for TAC).

Exposure	Incident CAC	Incident TAC
PM <sub>10</sub> (CTM)	1.23 (1.00, 1.52)	1.09 (0.90, 1.33)
PM <sub>10</sub> (LUR)	1.20 (1.02, 1.42)	0.98 (0.84, 1.13)
PM <sub>2.5</sub> (CTM)	1.06 (0.85, 1.33)	1.15 (0.94, 1.40)
PM <sub>2.5</sub> (LUR)	1.31 (1.06, 1.61)	1.06 (0.88, 1.28)
PN <sub>acc</sub> (CTM)	1.15 (0.95, 1.41)	1.15 (0.96, 1.37)
PM <sub>2.5abs</sub> (LUR)	1.11 (0.96, 1.29)	1.03 (0.91, 1.18)
NO <sub>2</sub> (CTM)	1.10 (0.91, 1.33)	1.08 (0.91, 1.28)
NO <sub>2</sub> (LUR)	1.21 (1.00, 1.47)	1.01 (0.84, 1.21)

Note: Main model is adjusted for age, sex, BMI, smoking status and quantity, ETS, LDL-C/HDL-C, physical activity, education, traffic noise and for dichotomous outcomes additionally years of follow-up; BMI, body mass index; CAC, coronary artery calcification; CI, confidence interval; CTM, chemistry transport modeling; ETS, environmental tobacco smoke; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LUR, land use regression; TAC, thoracic aortic calcification.

quality model. The CTM models average daily concentration of air pollutants in a 1 km<sup>2</sup> grid cell, based on emission factors, daily meteorology, and the distribution and chemical transformation of emissions (Hennig et al. 2016), reflecting long-term urban background concentrations taking changes in emission into account. In contrast, the LUR model estimates time-stable long-term air pollution concentrations, using a linear regression model. Urban background air pollution in a highly industrialized area close to coal-burning power plants and neighboring areas characterized by intensive livestock farming is expected to differ from air pollution at hot spots close to heavily trafficked roads, possibly contributing to differences in health effect estimates. Moreover, depending on the individual mobility of the participants, models reflecting urban background concentrations might lead to less exposure misclassification than point-specific models, specifically if emission patterns change during a long observation period. However, similar patterns of associations with subclinical atherosclerosis for both models remained, even when investigating participants less vs. more likely to exposure misclassification.

The estimated air pollution concentrations in this study were well below current European regulatory limits (EU 2008), suggesting that, even at current air pollution levels, adverse effects on the underlying pathology of CVD cannot be ruled out. In addition, observed results were robust with regard to adjustment for road traffic noise, a coexposure that has been shown to affect blood pressure (Kempen et al. 2018; Münzel et al. 2018), a major risk factor for the development of atherosclerosis. This finding was observed for all markers and in line with earlier studies that investigated thoracic calcification only (Hennig et al. 2019; Kälisch et al. 2013a). However, residual confounding of air pollution and noise cannot be ruled out due to possible noise exposure misclassification when using façade values and lack of personal exposure measures. Moreover, noise annoyance, which might play an additional role with regard to CVD, was not taken into account.

Our study has several limitations. For the measurement of TAC, no remeasurements for assessment of reliability were conducted, and the size of the measured area varied according to anatomical conditions, resulting in potentially large measurement error and imprecision of health effect estimation. cIMT ultrasound measurements were conducted by different examiners and followed two slightly different measurement protocols at t0 and t1, preventing the reader to identify the same location for cIMT reading at both time points. These differences increased random outcome measurement error and thereby contributed to imprecise health effect estimation. In addition, the relatively short time period between baseline and follow-up measurements (roughly 5 y) may have limited power to detect associations between air pollution exposure and progression of atherosclerosis. Exposure measurement error may have biased our estimates. First, long-term prebaseline exposure, which probably contributes most to the development of atherosclerosis during the follow-up period, was not available, and we used exposure during the examination periods (CTM) and time-stable estimates (LUR) as a surrogate for long-term air pollution exposure. Second, for assessing personal mobility, we had information only on employment status and on relocations within 5 y prior to baseline.

An important strength of our study is the relatively large study population with a comprehensive assessment of markers of subclinical atherosclerosis, in-depth covariate data. In addition, we applied two different commonly used air pollution models for estimating long-term air pollution exposure, reflecting urban background and point-specific exposure. Moreover, we considered traffic and noise, and we conducted comprehensive sensitivity analysis.

## Conclusions

Our study suggests that development and progression of subclinical atherosclerosis are associated with long-term air pollution in middle-aged participants with no or minor atherosclerotic burden at baseline, whereas overall no consistent associations are observed.

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## References

- Adar SD, Sheppard L, Vedal S, Polak JF, Sampson PD, Diez Roux AV, et al. 2013. Fine particulate air pollution and the progression of carotid intima-medial thickness: a prospective cohort study from the multi-ethnic study of atherosclerosis and air pollution. *PLoS Med* 10(4):e1001430, PMID: 23637576, <https://doi.org/10.1371/journal.pmed.1001430>.
- Agatston AS, Janowitz FWR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. 1990. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 15(4):827–832, PMID: 2407762, [https://doi.org/10.1016/0735-1097\(90\)90282-T](https://doi.org/10.1016/0735-1097(90)90282-T).
- Araujo J. A., Barajas B, Kleinman M, Wang X, Bennett BJ, Gong KW, et al. 2008. Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress. *Circ Res* 102(5):589–596, PMID: 18202315, <https://doi.org/10.1161/CIRCRESAHA.107.164970>.
- Bauer M, Möhlenkamp S, Lehmann N, Schermund A, Roggenbuck U, Moebus S, et al. 2009. The effect of age and risk factors on coronary and carotid artery atherosclerotic burden in males—results of the Heinz Nixdorf Recall Study. *Atherosclerosis* 205(2):595–602, PMID: 19200545, <https://doi.org/10.1016/j.atherosclerosis.2009.01.005>.
- Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, et al. 2013. Development of NO<sub>2</sub> and NO<sub>x</sub> land use regression models for estimating air pollution exposure in 36 study areas in Europe – The ESCAPE project. *Atmos Environ* 72:10–23, <https://doi.org/10.1016/j.atmosenv.2013.02.037>.
- de Hoogh K, Korek M, Vienneau D, Keuken M, Kukkonen J, Nieuwenhuijsen MJ, et al. 2014. Comparing land use regression and dispersion modelling to assess residential exposure to ambient air pollution for epidemiological studies. *Environ Int* 73:382–392, PMID: 25233102, <https://doi.org/10.1016/j.envint.2014.08.011>.
- Defilippis AP, Blaha MJ, Ndumele CE, Budoff MJ, Lloyd-Jones DM, McClelland RL, et al. 2011. The association of Framingham and Reynolds Risk Scores with incidence and progression of coronary artery calcification in MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 58(20):2076–2083, PMID: 22051329, <https://doi.org/10.1016/j.jacc.2011.08.022>.

- Den Ruijter HM, Peters SAE, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. 2012. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA* 308(8):796–803, PMID: 22910757, <https://doi.org/10.1001/jama.2012.9630>.
- Dorans KS, Wilker EH, Li W, Rice MB, Ljungman PL, Schwartz J, et al. 2016. Residential proximity to major roads, exposure to fine particulate matter, and coronary artery calcium. *Arterioscler Thromb Vasc Biol* 36(8):1679–1685, PMID: 27312220, <https://doi.org/10.1161/ATVBAHA.116.307141>.
- Dorans KS, Wilker EH, Li W, Rice MB, Ljungman PL, Schwartz J, et al. 2017. Residential proximity to major roads, exposure to fine particulate matter and aortic calcium: the Framingham Heart Study, a cohort study. *BMJ Open* 7: e013455, PMID: 28302634, <https://doi.org/10.1136/bmjopen-2016-013455>.
- Dragano N, Hoffmann B, Stang A, Moebus S, Verde PE, Weyers S, et al. 2009. Subclinical coronary atherosclerosis and neighbourhood deprivation in an urban region. *Eur J Epidemiol* 24(1):25–35, PMID: 18931923, <https://doi.org/10.1007/s10654-008-9292-9>.
- Eeftens M, Beelen R, Hoogh K, De Bellander T, Cesaroni G, Cirach M, et al. 2012. Development of Land Use Regression models for PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance, PM<sub>10</sub> and PM<sub>coarse</sub> in 20 European study areas; results of the ESCAPE project. *Environ Sci Technol* 46(20):11195–11205, PMID: 22963366, <https://doi.org/10.1021/es301948k>.
- Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al. 2010. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol* 56(17):1397–1406, PMID: 20946997, <https://doi.org/10.1016/j.jacc.2010.06.030>.
- EU (European Union). 2008. Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe. Off J Eur Union. <http://data.europa.eu/eli/dir/2008/50/oj> [accessed 24 September 2020].
- European Environment Agency. 2011. Index to methodology chapters ordered by SNAP97 Activity. <http://www.eea.europa.eu/publications/EMEPCORINAIR4/page009-a.html> [accessed 30 November 2015].
- Foerch C, Buehler A, von Kegler S, Sitzer M. 2003. Intima-media thickness side differences are limited to the common carotid artery. *Hypertension* 42(6):e17, PMID: 14674381, <https://doi.org/10.1161/01.HYP.0000103164.73172.30>.
- Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, et al. 2008. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med* 168(12):1333–1339, PMID: 18574091, <https://doi.org/10.1001/archinte.168.12.1333>.
- Franklin BA, Brook R, Arden Pope C 3rd. 2015. Air pollution and cardiovascular disease. *Curr Probl Cardiol* 40(5):207–238, PMID: 25882781, <https://doi.org/10.1016/j.cpcardiol.2015.01.003>.
- Gakidou E, Afshin A, Abajobir AA, Abate KH, Abbafati C, Abbas KM, et al. 2017. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 390(10100):1345–1422, PMID: 28919119, [https://doi.org/10.1016/S0140-6736\(17\)32366-8](https://doi.org/10.1016/S0140-6736(17)32366-8).
- Gan WQ, Allen RW, Brauer M, Davies HW, Mancini GBJ, Lear S. A. 2014. Long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis: a prospective cohort study. *BMJ Open* 4(4):e004743, PMID: 24710134, <https://doi.org/10.1136/bmjopen-2013-004743>.
- Geisel MH, Bauer M, Hennig F, Hoffmann B, Lehmann N, Möhlenkamp S, et al. 2017. Comparison of coronary artery calcification, carotid intima-media thickness and ankle-brachial index for predicting 10-year incident cardiovascular events in the general population. *Eur Heart J* 38(23):1815–1822, PMID: 28379333, <https://doi.org/10.1093/eurheartj/ehx120>.
- Greenland S, Pearl J, Robins JM. 1999. Causal diagrams for epidemiologic research. *Epidemiology* 10(1):37–48, PMID: 9888278.
- Hennig F, Moebus S, Reinsch N, Budde T, Erbel R, Jo K, et al. 2019. Investigation of air pollution and noise on progression of thoracic aortic calcification: results of the Heinz Nixdorf Recall Study. *Eur J Prev Cardiol* 0:1–10, <https://doi.org/10.1177/2047487319854818>.
- Hennig F, Sugiri D, Tzivian L, Fuks K, Moebus S, Jöckel K-H, et al. 2016. Comparison of land-use regression modeling with dispersion and chemistry transport modeling to assign air pollution concentrations within the Ruhr area. *Atmosphere* (Basel). 7(3):48, <https://doi.org/10.3390/atmos7030048>.
- Hoffmann B, Weinmayr G, Hennig F, Fuks K, Moebus S, Weimar C, et al. 2015. Air quality, stroke, and coronary events. *Dtsch Arztebl Int* 115:195–201, <https://doi.org/10.3238/arztebl.2015.0195>.
- Kälsch H, Hennig F, Moebus S, Möhlenkamp S, Dragano N, Jakobs H, et al. 2013a. Are air pollution and traffic noise independently associated with atherosclerosis: the Heinz Nixdorf Recall Study. *Eur Heart J* 35(13):853–860, PMID: 24194529, <https://doi.org/10.1093/eurheartj/ehx426>.
- Kälsch H, Lehmann N, Moebus S, Hoffmann B, Stang A, Jöckel KH. 2017. Aortic calcification onset and progression: association with the development of coronary atherosclerosis. *J Am Heart Assoc* 6(4):e005093, <https://doi.org/10.1161/JAHA.116.005093>.
- Kälsch H, Lehmann N, Möhlenkamp S, Hammer C, Mahabadi AA, Moebus S, et al. 2013b. Prevalence of thoracic aortic calcification and its relationship to cardiovascular risk factors and coronary calcification in an unselected population-based cohort: the Heinz Nixdorf Recall Study. *Int J Cardiovasc Imaging* 29(1):207–216, PMID: 22527262, <https://doi.org/10.1007/s10554-012-0051-3>.
- Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, et al. 2016. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. *Lancet* 388(10045):696–704, PMID: 27233746, [https://doi.org/10.1016/S0140-6736\(16\)00378-0](https://doi.org/10.1016/S0140-6736(16)00378-0).
- Kempen EV, Casas M, Pershagen G, Foraster M. 2018. WHO Environmental Noise Guidelines for the European Region: a systematic review on environmental noise and cardiovascular and metabolic effects: a summary. *Int J Environ Res Public Health* 15(2):379, PMID: 29470452, <https://doi.org/10.3390/ijerph15020379>.
- Künzli N, Jerrett M, Garcia-Esteban R, Basagaña X, Beckermann B, Gilliland F, et al. 2010. Ambient air pollution and the progression of atherosclerosis in adults. *PLoS One* 5(2):e0096, PMID: 20161713, <https://doi.org/10.1371/journal.pone.0009096>.
- Künzli N, Perez L, Klot SV, Baldassarre D, Bauer M, Basagana X, et al. 2011. Investigating air pollution and atherosclerosis in humans: concepts and outlook. *Prog Cardiovasc Dis* 53(5):334–343, PMID: 21414468, <https://doi.org/10.1016/j.pcad.2010.12.006>.
- Lehmann N, Erbel R, Mahabadi AA, Rauwolf M, Möhlenkamp S, Moebus S, Kälsch H, et al. 2018. Value of progression of coronary artery calcification for risk prediction of coronary and cardiovascular events result of the HNR Study (Heinz Nixdorf Recall). *Circulation* 137(7):665–679, PMID: 29142010, <https://doi.org/10.1161/CIRCULATIONAHA.116.027034>.
- Luo X, Yang Y, Cao T, Li Z. 2011. Differences in left and right carotid intima-media thickness and the associated risk factors. *Clin Radiol* 66(5):393–398, PMID: 21324442, <https://doi.org/10.1016/j.crad.2010.12.002>.
- Memmesheimer M, Frieze E, Ebel A, Jakobs HJ, Feldmann H, Kessler C, et al. 2004. Long-term simulations of particulate matter in Europe on different scales using sequential nesting of a regional model. *Int J Environ Pollut* 22(1/2):108–132, <https://doi.org/10.1504/IJEP.2004.005530>.
- Münzel T, Schmidt FP, Steven S, Herzog J, Daiber A, Sørensen M. 2018. Environmental noise and the cardiovascular system. *J Am Coll Cardiol* 71(6):688–697, PMID: 29420965, <https://doi.org/10.1016/j.jacc.2017.12.015>.
- Nair SB, Malik R, Khattar RS. 2012. Carotid intima-media thickness: ultrasound measurement, prognostic value and role in clinical practice. *Postgrad Med J* 88(1046):694–699, PMID: 22761324, <https://doi.org/10.1136/postgradmedj-2011-130214>.
- Nonnemacher M, Jakobs H, Viehmann A, Vanberg I, Kessler C, Moebus S, et al. 2014. Spatio-temporal modelling of residential exposure to particulate matter and gaseous pollutants for the Heinz Nixdorf Recall Cohort. *Atmos Environ* 91:15–23, <https://doi.org/10.1016/j.atmosenv.2014.03.052>.
- O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK. 1999. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *Cardiovascular Health Study Collaborative Research Group. N Engl J Med* 340(1):14–22, PMID: 9878640, <https://doi.org/10.1056/NEJM199901073400103>.
- Peinemann F, Moebus S, Dragano N, Möhlenkamp S, Lehmann N, Zeeb H, et al. 2011. Secondhand smoke exposure and coronary artery calcification among nonsmoking participants of a population-based cohort. *Environ Health Perspect* 119(11):1556–1561, PMID: 21742575, <https://doi.org/10.1289/ehp.1003347>.
- Perez L, Wolf K, Hennig F, Penell J, Basagaña X, Aguilera I, et al. 2015. Air pollution and atherosclerosis: a cross-sectional analysis of four European cohort studies in the ESCAPE Study. *Environ Health Perspect* 123(6):597–605, PMID: 25625785, <https://doi.org/10.1289/ehp.1307711>.
- Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB. 2011. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med* 365(3):213–221, PMID: 21774709, <https://doi.org/10.1056/NEJMoa1012592>.
- Provost EB, Madhloum N, Panis LI, De Boever P, Nawrot TS. 2015. Carotid intima-media thickness, a marker of subclinical atherosclerosis, and particulate air pollution exposure: the meta-analytical evidence. *PLoS One* 10(5):e0127014, <https://doi.org/10.1371/journal.pone.0127014>.
- Rückerl R, Schneider A, Breitner S, Cyrys J, Peters A. 2011. Health effects of particulate air pollution: a review of epidemiological evidence. *Inhal Toxicol* 23(10):555–592, PMID: 21864219, <https://doi.org/10.3109/08958378.2011.593587>.
- Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, et al. 2002. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. *Am Heart J* 144(2):212–218, PMID: 12177636, <https://doi.org/10.1067/mhj.2002.123579>.

- Soares RSC, Carvalho-Oliveira R, Ramos-Sanchez E, Catanozi S, Fernando L, Mauad T, et al. 2009. Air pollution and antibodies against modified lipoproteins are associated with atherosclerosis and vascular remodeling in hyperlipemic mice. *Atherosclerosis* 207(2):368–373, PMID: 19486979, <https://doi.org/10.1016/j.atherosclerosis.2009.04.041>.
- Stang A, Moebus S, Dragano N, Beck EM, Mo S, Schmermund A, et al. 2005. Baseline recruitment and analyses of nonresponse of the Heinz Nixdorf Recall Study: identifiability of phone numbers as the major determinant of response. *Eur J Epidemiol* 20(6):489–496, PMID: 16121757, <https://doi.org/10.1007/s10654-005-5529-z>.
- Sun Q, Wang A, Jin X, Natanzon A, Duquaine D, Brook RD. 2005. Acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA* 294(23):3003–3010, <https://doi.org/10.1001/jama.294.23.3003>.
- U.S. EPA (U.S. Environmental Protection Agency). 2019. Integrated Science Assessment for Particulate Matter.
- UNESCO (United Nations Educational, Scientific and Cultural Organisation). 1997. International standard classification of education ISCED 1997. <https://unesdoc.unesco.org/ark:/48223/pf0000146967.locale=en> [accessed 24 September 2020].
- Wang M, Sampson PD, Sheppard LE, Stein JH, Vedal S, Kaufman JD. 2019. Long-term exposure to ambient ozone and progression of subclinical arterial disease: the Multi-Ethnic Study of Atherosclerosis and air pollution. *Environ Health Perspect* 127(5):57001, PMID: 31063398, <https://doi.org/10.1289/EHP3325>.
- Wendelhag I, Liang Q, Gustavsson T, Wikstrand J. 1997. A new automated computerized analyzing system simplifies readings and reduces the variability in ultrasound measurement of intima-media thickness. *Stroke* 28(11):2195–2200, PMID: 9368564, <https://doi.org/10.1161/01.str.28.11.2195>.
- WHO (World Health Organization). 2009. Global health risks mortality and burden of disease attributable to selected major risks: Technical Report [Internet]. Copenhagen: WHO Regional Office for Europe. <https://www.ncbi.nlm.nih.gov/books/NBK361805/> [accessed 24 September 2020].
- WHO Regional Office for Europe. 2013. Review of evidence on health aspects of air pollution—REVIHAAP Project. <https://www.ncbi.nlm.nih.gov/books/NBK361805/> [accessed 24 September 2020].
- WHO. 2013. ATC/DDD Index 2018. [http://www.whocc.no/atc\\_ddd\\_index/](http://www.whocc.no/atc_ddd_index/) [accessed 24 September 2020].
- Wilker EH, Mittleman M. A, Coull B. A, Gryparis A, Bots ML, Schwartz J, et al. 2013. Long-term exposure to black carbon and carotid intima-media thickness: the normative aging study. *Environ Health Perspect* 121(9):1061–1067, PMID: 23820848, <https://doi.org/10.1289/ehp.1104845>.
- Wilker EH, Preis SR, Beiser AS, Wolf PA, Au R, Kloog I, et al. 2015. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. *Stroke* 46(5):1161–1166, PMID: 25908455, <https://doi.org/10.1161/STROKEAHA.114.008348>.